response. Applicants respectfully submit that this supports claims generically encompassing these and other methods; in addition, claims directed to specific means for immunization should be allowed. Applicants have repeatedly pointed to their evidence regarding direct injection; clarification is respectfully requested as to why the Examples, which clearly show the efficacy of direct injection, are not deemed enabling of the direct injection mode of practicing the present invention.

The Office Action further states that the evidence demonstrates that biolistic injection into skin according to the present invention results in a CTL-mediated immune response to tumor or virus. While Applicants appreciate the acknowledgement that this particular embodiment of the invention is enabled, they disagree that the claims should be limited to biolistic injection only to skin. As noted above, the examples provide evidence that direct injection is also an effective means of immunization according to the present invention. Accordingly, the examples also provide evidence that injection to points other than skin are effective. (See, for example, Example Section 7, page 25, lines 25-29 which discusses subcutaneous injection.) As such, the claims should not be limited to skin. Applicants respectfully request clarification as to why the Examples, which clearly show the efficacy of administration to points other than skin, are deemed not enabling for administration other than to skin.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5-17, 19-32, 34-47, 49-61 and 63-71 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is respectfully traversed.

The Office Action rejects the claims based on the use of the language "capable of generating an immune response", and states that this merely shows a latent characteristic of the mammalian host and as such carries no patentable weight. The Examiner has suggested using language to indicate that the mammalian host is fully immunocompetent, i.e. with a fully functional immune system intact. Applicants respectfully disagree that their added language is inappropriate, and further that the suggested language is appropriate.

The present invention is directed to any mammalian host capable of mounting an immune response, including those who are less than fully immunocompetent. Indeed, limiting the invention to those who are fully immunocompetent would prevent this invention's therapeutic use on cancer patients who are less than fully immunocompetent, yet are still capable of mounting some immune response using the present methods (or any other treatment). In addition, Applicants submit that the phrase "capable of generating an immune response" describes the mammalian host to whom the present methods are directed; hosts incapable of generating an immune response would not be appropriately treated by the present methods. Thus, the added language does more than identify a "latent

characteristic" of the host. Even if it did, which Applicants do not concede, Applicants fail to see how using language such as "fully immunocompetent" is any less a description of a latent characteristic than the phrase "capable of generating an immune response".

In addition, Applicants note that the language "capable of generating an immune response" was allowed in the claims of US Patent No. 5,951,975. Applicants respectfully request that claims using language "capable of generating an immune response" be allowed here as well.

Rejections Under 35 U.S.C. § 102

Claims 1, 15, 29, and 68-71 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by either Tang et al. (Nature, 1992) or Barry et al. (Biotechniques, 1994). This rejection is respectfully traversed.

The present invention, as recited in amended Claims 1, 15 and 29, is now directed to methods of eliciting a primary CTL-based immune response. In contrast, both Tang et al. and Barry et al. teach only the elicitation of antibody responses. The mechanism by which an antibody response is triggered is different from that in which a CTL response is elicited. Antibody responses are not related to class I presentation and antibody responses require class II presentation to helper T-cells, not to CTLs. Antibody responses further require that the protein be recognized by B-cells. Thus, the APC must have an external source of antigenic protein. In the present invention, the source of antigen is internal to the APC, i.e., produced by the APC receiving the delivered DNA. Thus, targeting delivery of DNA to the cytoplasm of APCs targets class I presentation of the antigen and the induction of primary CTL responses. This is not taught in any of the cited references. Thus, the methods of Tang et al. and Barry et al. teach a different result. To anticipate under 35 U.S.C. § 102, a reference must show all of the elements of a claim.

In addition, neither Tang et al. nor Barry et al. teaches the use of direct injection; Claim 29 is specifically directed to this method. Contrary to the Examiner's assertion that the "biolistic system requires that DNA be directly injected into the skin," direct injection via hypodermic needle and injection with a biolistic device are two distinct methods of injection which do not overlap. The gene gun is an expensive and sophisticated instrument which requires a helium tank to supply velocity. DNA coated particles injected via the biolistic system are forced into the cells, thus circumventing uptake of the DNA by cell membranes. In contrast, injection via hypodermic needle results in the deposit of particles in the extracellular fluid, where cells (such as APCs) capable of uptake through phagocytosis absorb the particles. Hence, Tang et al. and Barry et al. do not teach direct injection.

Applicants further note that with regard to the rejection under 35 U.S.C. § 102 the Office Action is equating the biolistic system and direct injection; in the rejection under 35 U.S.C. § 112, however, the Office Action maintains the

position that use of a biolistic device and direct injection are distinct. Clarification of this apparent discrepancy is respectfully requested.

Claims 1, 15 and 29 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hui et al. (Journal of Immunological Methods). This rejection is respectfully traversed.

As amended, the claims of the present invention are directed to a method of immunization which produces a primary CTL immune response *in vivo*. Hui et al. does not teach such a result. Rather, Hui teaches an allo-antigenic response. Moreover, the passage cited in the Office Action refers to elicitation of a secondary CTL response, not a primary response as is now claimed by Applicants. As noted previously, Hui does not show APC transfection or direct injection of particulate DNA; Hui is limited to use of a biolistic device. Thus, several aspects of the presently claimed invention are not taught by Hui; because these aspects are lacking in the reference, it is not appropriately cited under 35 U.S.C. § 102(b), which requires that all of the elements of a claim be present in a single reference.

Rejections Under 35 U.S.C. § 103

Claims 1-3, 5-17, 19-32, 49-61 and 63-71 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner et al. (U.S. Patent No. 5,593,972) in view of either Tang et al. or Barry et al. This rejection is respectfully traversed.

As amended, Applicants believe the claims are no longer obvious in view of the above-cited references. None of the above references teach or suggest the methods by which APCs are specifically targeted for transfection. Weiner et al. discloses only intramuscular injection; Tang et al. and Barry et al. disclose only an antibody response. Nothing in these references, taken singly or together, teaches or suggests that genetic immunization will produce a primary CTL response as claimed in the present invention.

Thus, Applicants respectfully submit that the references cited in the Office Action do not combine to render the present invention obvious.

SUMMARY

For all of the above reasons, Applicants submit that the currently pending claims are enabled by the specification, as filed. In addition, it is submitted that the art of record does not anticipate or teach the claimed methods. Applicants

respectfully submit, therefore, that the above claims are in condition for a Notice of Allowance; such action is respectfully requested at an early date.

Respectfully submitted,

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